A case of Type A insulin resistance syndrome in a 14-year-old girl without common clinical features

Running title: Type A insulin resistance syndrome with INSR gene mutation

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Abstract

Type A insulin resistance syndrome is a rare congenital disorder caused by insulin receptor dysfunction arising from heterozygous mutations in the insulin receptor (INSR) gene. It is usually diagnosed in non-obese female adolescents with insulin resistance, acanthosis nigricans, or ovarian hyperandrogenism. We present the case of a 14-year-old adolescent girl with non-obesity diabetes and insulin resistance; however, she had no acanthosis nigricans, or menstrual abnormalities. The laboratory results were as follows: fasting plasma glucose 179 mg/dL; C-peptide 1.8 ng/mL; insulin 34.8 IU/mL; HbA1c 10.6%. Islet cell autoantibodies, insulin autoantibodies, and glutamic acid decarboxylase antibodies were negative. We performed a next-generation sequencing-based targeted gene panel for the known maturity-onset diabetes of the young and found a heterozygous mutation in the INSR gene c.3602G>A (p.Arg1201Gln). Her mother carried the same mutation as her and also did not present with acanthosis nigricans or menstruation abnormalities. Type A insulin resistance syndrome has diverse clinical phenotypes even with the same type of mutation at the same site in the INSR gene. Clinicians should consider genetic testing for early detection and adequate treatment approaches.

Keywords: Diabetes mellitus, Insulin resistance, Insulin receptor
Introduction

The insulin receptor (INSR) is a transmembrane protein, composed of two α- and two β-subunits. Insulin binds to the extracellular α-subunits and leads to the activation of tyrosine kinase at the intracellular β subunit, and the autophosphorylation of the receptor, followed by the activation of signal transduction cascades. The INSR gene is located at 19p13.2 and has 22 exons, which encode for both the α- (exons 1–11) and β- subunits (exons 12–22). Mutations in the INSR gene cause a broad spectrum of inherited insulin resistance syndromes as a result of insulin receptor dysfunction. More than 100 diseases caused by mutations in INSR gene have been identified. Homozygous or compound heterozygous mutations in the α-subunit result in more severe insulin resistance (Donohue syndrome, Rabson–Mendenhall syndrome) with a recessive pattern of inheritance. In contrast, heterozygous mutations in the β-subunit lead to milder insulin resistance with a dominant negative effect, which is common in patients with type A insulin resistance syndrome (IRS)1. Most mutations located outside the tyrosine kinase (TK) domain are thought to impair insulin receptor activity incompletely. Most asymptomatic carriers discovered by familial studies of Donohue syndrome and Rabson–Mendenhall syndrome have mutations outside the TK domain. Mutations in the TK domain impair insulin receptor activity more critically than those located in other domains. In patients with Type A IRS, INSR mutations were located in the TK domain of the β-subunit2.

Unlike most people with insulin resistance, individuals with type A IRS are usually not obese. Type A IRS is characterized by the triad of insulin resistance, acanthosis nigricans (AN), and ovarian hyperandrogenism. The disorder most commonly comes into medical attention around puberty due to the symptoms arising from ovarian dysfunction, which drives synergy between gonadotropin and insulin action on the ovaries3,4. This report presents the case of a non-obese adolescent girl diagnosed with diabetes mellitus (DM) at 14 years of age and had no AN, hirsutism, or menstrual abnormalities.
Her mother had the same mutation as her, but did not present with AN, hirsutism, or menstruation abnormalities.

**Case report**

A 14.2-year-old adolescent girl with diabetes mellitus was referred to our clinic. Glucosuria was detected in school urinary screening test two months prior, but she did not undergo evaluation. Subsequently, polyuria and polydipsia developed. At presentation, she was not obese with a height of 153.0 cm (standard deviation score [SDS] –1.02), weight of 46.5 kg (SDS –0.6), and body mass index (BMI) of 19.9 kg/m² (SDS –0.2). Her blood pressure was 110/70 mmHg. She did not have a dysmorphic face, except for dental abnormalities, including crowding of the upper and lower teeth. Physical examination revealed no abnormalities. The patient had no facial acne or acanthosis nigricans. Black, coarse, excess hair was observed on the patient’s upper lip, chin, midline of the lower abdominal wall, and arm (modified Ferriman–Gallwey score of 7). Hirsutism was defined as a value ≥ 85).

She was born at a gestational age of 40 weeks with a birth weight of 3100 g. According to her mother, she has had darkened skin color and hypertrichosis on her extremities since birth. At the age of 8, spontaneous thelarche occurred. She had received the GnRH agonist treatment for central precocious puberty for 2.5 years at our hospital. At the age of 13 years, she had menarche which was one year after the GnRH agonist treatment had ended. Her menstrual cycle was regular.

Laboratory findings were as follows: hemoglobin 13.6 g/dL, white blood cell count 5500/mm³, platelet 295,000/mm³, aspartate transaminase (AST) 13 IU/L, alanine transaminase (ALT) 11 IU/L, total cholesterol 160 mg/dL, HbA1c 10.6%, fasting plasma glucose 179 mg/dL, fasting C-peptide 1.8 ng/mL (reference range, 1.1-4.4 ng/mL), fasting insulin 34.8 μU/mL (reference range, 2.6–24.9
μU/mL), and Homeostatic Model Assessment for Insulin Resistance score (HOMA-IR) 15.4 (cut-off value, ≥ 3.6) (table 1). Islet cell autoantibodies (ICA), insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD), and anti-microsomal and anti-thyroglobulin antibodies were negative. Because of the suspicion of monogenic diabetes, we performed next-generation a sequencing-based targeted gene panel for known maturity-onset diabetes of the young, which encompassed 32 related genes (ABCC8, APPL1, BLK, CEL, EIF2AK3, FOXP3, GATA4, GATA6, GCK, GLIS3, HNF1A, HNF1B, HNF4A, IER3IP1, INS, INSR, KCNJ11, KLF11, MNX1, NEUROD1, NEUROG3, NIKX2-2, PAX4, PAX6, PDX1, PTF1A, PTRRD, PFX6, SLC19A2, SLC2A2, SYT9, and WFS1), using MiSeqDX (Illumina, Inc.). A heterozygous mutation in INSR (c.3602G>A (p.Arg1201Gln)) was identified (fig. 1). This is previously reported as p.Arg1174Gln according to the classical numbering system. The same mutation (c.3602G>A) was also found in the proband's mother. The mother was non-obese (162 cm, 43 kg, BMI 16.38 kg/m²) and had a history of gestational diabetes mellitus that required insulin treatment during both pregnancies. The mother’s diabetes mellitus improved after delivery. She did not have AN, hirsutism, or previous menstrual abnormalities. She had no diabetes–related symptoms. However, her fasting blood glucose was 100–150 mg/dL, and her postprandial blood glucose was 200 or more, and she started taking diabetes medications at a local medical center. The mutation was not identified in the proband’s father (178 cm, 80 kg, BMI 25.2 kg/m²) who did not have any diabetic symptoms.

Although the patient had a mutation in the INSR gene, she had normal levels of serum luteinizing hormone (LH) 2.8 mIU/mL, follicular stimulating hormone (FSH) 7.8 mIU/mL, estradiol 39.7 pg/mL, progesterone 0.28 ng/mL, testosterone 0.2 ng/mL (reference range 0.2-0.38 ng/mL [sexual maturity rating (SMR) 5]), free testosterone 0.64 pg/mL (reference range 1.1-6.3 pg/mL), dehydroepiandrosterone-sulfate (DHEA-S) 107.33 ug/dL (reference range 44-248 ug/dL), 17α-OH-
progesterone 1.15 ng/mL (reference range 0.1-9.5 ng/mL [SMR 5]), and sex hormone binding globulin (SHBG) 86.65 nmol/L (reference range 18.2-135.5 nmol/L).

Metformin and self-injection with insulin was initiated. Insulin therapy was discontinued because of frequent hypoglycemia. Diet and exercise therapy with metformin improved HbA1c levels to 6.8%. During the follow up period, her weight increased to 53 kg and her HbA1c level increased to 8.1% due to increased snacking. After the dose of metformin had been increased to 2 g/day and voglibose 0.6 mg/day was started in addition to the lifestyle interventions, the HbA1c level improved to 7%. Serum liver function, lipid profile, and testosterone levels were within the normal range. No AN or diabetic complications were observed. The modified Ferriman–Gallwey score remained at 7, which was not higher than before. However, a 75g oral glucose tolerance test still showed hyperglycemia (fasting plasma glucose 122 mg/dL, 2-hour glucose 275 mg/dL) with hyperinsulinemia (fasting insulin 23.9 μIU/mL, 2-hour insulin 123 μIU/mL).

Discussion

Type A IRS is usually diagnosed in non-obese female adolescents or young women with AN, hirsutism, or oligomenorrhea with polycystic ovaries. At presentation, hyperglycemia is often not observed. When the β-cell’s compensatory response to insulin resistance is insufficient to regulate glucose metabolism, impaired glucose tolerance and diabetes mellitus develop, but rarely present with hypoglycemia. Type A IRS can be misdiagnosed as polycystic ovary syndrome (PCOS). AN is a cutaneous manifestation of chronic hyperinsulinemia. The extent and severity of AN may be correlated with the degree of IR. High concentrations of insulin interact with insulin-like growth factor receptors, triggering the proliferation of keratinocytes and fibroblasts, and resulting in AN. Although AN is commonly observed in most patients with type A IRS, type A IRS without AN has
also been reported. The reason for the absence of AN in some patients with type A IRS is still unknown\textsuperscript{9)\textsuperscript{9)\textsuperscript{9)}}.

The mutation in this patient has previously been reported\textsuperscript{10-12)\textsuperscript{10-12)}\textsuperscript{12)}\textsuperscript{12)}. It has also been reported in women with symptomatic hypoglycemia. Hyperinsulinemia with impaired insulin clearance has been suggested to rescue genetically altered insulin signaling in the liver and/or muscles. The symptoms of hypoglycemia decrease with metformin medication\textsuperscript{13)}.\textsuperscript{13)}

There is a diversity of clinical phenotypes, even with the same type of mutation at the same site in the \textit{INSR} gene\textsuperscript{14-15)\textsuperscript{14-15)}. It is diagnosed more often in women than in men because women have more health problems associated with hyperandrogenism. In the prediabetic phase, males exhibit only AN and sometimes hypoglycemia, and they often remain undiagnosed even after the development of symptomatic diabetes. It is probably diagnosed as type 2 diabetes in mid-life\textsuperscript{3,4)\textsuperscript{3,4)}. In women, the features of type A IRS often do not become apparent until puberty or later. Type A IRS is not usually diagnosed during childhood\textsuperscript{3,4)\textsuperscript{3,4)}. Only a few cases of childhood diagnoses have been reported. Wei et al\textsuperscript{16)\textsuperscript{16)} reported two cases who presented with type A IRS in childhood: one patient was an 11.8-year-old prepubertal non-obese diabetic girl (p.Pro1236Ala) without AN or other signs of hyperandrogenism, and the second patient was a 7.3-year-old non-obese girl (p.Pro1205Leu) who presented with pubic hair development and was diagnosed with premature adrenarche. At 12.5 years, the second patient presented with AN, hirsutism, and acne, but without obesity. Oral glucose tolerance testing (OGTT) revealed fasting hypoglycemia and 2-hour hyperglycemia with severe hyperinsulinemia. Ariza et al\textsuperscript{17)\textsuperscript{17)} reported an 8-year-old non-obese boy with diabetes who did not show AN at the first visit and was lost to follow-up. Five years later, he was seen again and showed sustained postprandial hyperglycemia, sporadic preprandial hypoglycemia, and AN, despite having a normal BMI. Although it is known that most patients with type A IRS are not obese, Takasawa et al\textsuperscript{2)\textsuperscript{2)}}
reported an 11-year-old obese boy (BMI 25.3; SDS +1.8) with AN and severe insulin resistance.

In those with severe insulin resistance, puberty is often accelerated, most likely due to the action of hyperinsulinemia, which exerts synergistic effects with gonadotrophins on the ovaries\textsuperscript{3,4}. However, no cases of type A IRS with precocious puberty have been reported. The patient in this study was treated for central precocious puberty, but she has no menstrual abnormalities until now. Her mother with the same mutation did not have a precocious puberty or menstrual abnormalities; therefore, we could not conclude that the insulin resistance of this patient was related to central precocious puberty.

In our study, the patient did not exhibit dyslipidemia. The absence of dyslipidemia or fatty liver is suggestive of primary insulin receptopathy\textsuperscript{3,4}. In adults with insulin resistance, type 2 diabetes mellitus, and obesity, plasma adiponectin levels are reduced. In contrast, adiponectin levels have been found to be paradoxically increased in subjects with insulin receptopathy. Defective insulin action on adipocytes has been suggested to increase adiponectin levels\textsuperscript{3,4}. The absence of dyslipidemia and fatty liver disease and inappropriately normal or elevated plasma adiponectin levels are characteristic clinical features in patients with severe insulin resistance due to mutation in $INSR$\textsuperscript{3,4}.

Although type A IRS is rare in clinical practice, it is presumed that many patients are overlooked\textsuperscript{2}. Treatment of type A IRS remains largely empirical. It aims to prevent long-term complications of diabetes and improve hyperandrogenism. Although metformin has limited efficacy, it should be introduced early if severe hyperinsulinemia persists, and can be beneficial at high doses. Thiazolidinediones, acarbose, and leptin are also used. Glucagon-like peptide 1 agonists and dipeptidyl peptidase IV inhibitors may be effective. As diabetes progresses, patients who are not controlled by oral hypoglycemic agents may require the use of high doses of exogenous insulin with limited effect\textsuperscript{18,19}. Despite acceptable control during adolescence, long-term metabolic control has been reported to be poor, and diabetes complications are frequent in patients with type A IRS\textsuperscript{20}.  


Therefore, early diagnosis and adequate management are important.

In conclusion, because of the variable presentation and subtle clinical signs, particularly in childhood, clinicians should consider genetic testing for early diagnosis and adequate treatment approaches for type A IRS in patients with DM, who lack both characteristics of type 1 DM (islet autoantibodies, low c-peptide) and type 2 DM (obese, dyslipidemia, fatty liver), or in non-obese patients with IR and ovarian hyperandrogenism.

Acknowledgments

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References


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Ethical statement

This report was approved by the Institutional Review Board of the Daegu Catholic University Medical Center, Daegu, Korea (IRB No. CR-21-061-L). The informed consent was obtained from the patient and patient's parents for the preparation and publication of this case report.

Notes

Conflicts of interest: No potential conflict of interest relevant to this article was reported.

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Table 1. Levels of HbA1c, insulin, and sex hormone during follow-up.

HbA1c: glycated hemoglobin, F-glc; fasting glucose, F-ins; fasting insulin, T-chol; total cholesterol, TG; triglyceride, LH; luteinizing hormone, FSH; follicular stimulating hormone, T; testosterone. *; initial visit
Fig. 1. Sequencing results for mutation in the *INSR* gene of the patient and her parents. A heterozygous G to A transition at nucleotide 3602 of the *INSR* gene (c.3602G>A) resulting in a missense change of Arginine with Glutamine at amino acid 1201 (p.Arg1201Gln) was identified in the proband and mother, but not in the father.
Table 1. Levels of HbA1c, insulin and sex hormone during follow-up.

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HbA1c; glycated hemoglobin, F-glucose, F-insulin, T-cholesterol, TG; triglyceride, LH; luteinizing hormone, FSH; follicular stimulating hormone, T; testosterone. *; initial visit.
INSR NM_000208.3:c.3602G>A (p.Arg1201Gln)